

## REMARKS

### Status of the Claims

#### *Pending claims*

Claims 1 to 7, 9 to 12, 16, 17, 28 to 44, 46 to 49, 51 to 53 and 55 are pending and under consideration. Claims 34, 35, 38 and 44 have been withdrawn. Thus, claims 1 to 7, 9 to 12, 16, 17, 28 to 33, 36, 37, 39 to 43, 46 to 49, 51 to 53 and 55 are pending and under consideration.

#### *Allowed claim*

Applicants thank the Examiner for finding claim 16 allowable.

#### *Claims amended the instant amendment*

Claim 12 has been amended. Thus, after entry of the instant amendment, claims 1 to 7, 9 to 12, 16, 17, 28 to 33, 36, 37, 39 to 43, 46 to 49, 51 to 53 and 55 will be pending and under consideration.

Applicants respectfully request entry of the amendments set forth in this response. The amendment places the case in condition for allowance and places the case in better condition for appeal; the amendment does not raise any issues of new matter and does not present new issues requiring further consideration or search.

### Telephonic Interview

Applicants thank Examiner Hutson for the helpful telephonic interview of June 14, 2007, in which, in brief summary, the outstanding objections and rejections were discussed. As suggested by the Examiner, Applicants have included arguments in the present response directed to showing enablement for the pending claims, particularly for those claims directed to nucleic acids comprising 95% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity.

### Outstanding Objections and Rejections

Claims 3 and 12 have been objected to.

The rejection of claims 1, 2, 4 to 7, 9 to 11, 28 to 33, 36, 37, 39 to 43, 46 to 49, 51 to 53

and 55, under 35 U.S.C. §112, first paragraph, is maintained (enablement requirement).

Applicants respectfully traverse all outstanding objections to the claims and rejection of the claims.

#### Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the amended claims in this and previous responses.

#### Claim Objections

The Office has objected to claim 3 as being dependent upon rejected claim 1. As the instant response addresses the rejection of claim 1, the objection to claim 3 can be removed.

The Office has shown concern for the wording of part (b) of claim 12. The instant amendment addresses this issue.

#### Issues under 35 U.S.C. §112, first paragraph

The rejection of claims 1, 2, 4 to 7, 9 to 11, 28 to 33, 36, 37, 39 to 43, 46 to 49, 51 to 53 and 55, under 35 U.S.C. §112, first paragraph, is maintained because the specification allegedly does not reasonably provide enablement for the claimed invention, for reasons set forth in detail on pages 3 to 5, of the OA.

The Office states that the specification is enabling for the nucleic acid comprising SEQ ID NO:1 and encoding a polypeptide having polymerase activity. However, it is alleged, that the specification does not provide guidance for the production of the encompassed nucleic acids. The Office indicates on page 4 of the OA that Applicants have provided some guidance, but that it is insufficient to enable the currently claimed nucleic acids which have identity to SEQ ID NO:1. The Office alleges that extended experimentation would be required to determine which substitutions would be acceptable to retain the desired activity/function and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable.

Applicants respectfully traverse and maintain that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, the genus of nucleic acids encoding polypeptides having polymerase activity, including nucleic acids having at least 95% sequence identity to SEQ ID NO:1. As discussed in Applicants previous responses, Applicants maintain that the specification did provide the skilled artisan with a reasonable amount of guidance with respect to production of and screening for nucleic acids with at least 95% sequence identity to SEQ ID NO:1 which encode polypeptides having polymerase activity.

Applicants addressed this issue in their previous responses in, inter alia, an expert declaration where Dr. Short declared that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art for screening enzymes for polymerase activity was very high. Dr. Short declared that it would not have been necessary for the skilled artisan to understand which specific regions of the polymerase sequence or structure needed to be modified without affecting function or activity to routinely generate the genus of polypeptides used in the claimed methods. Dr. Short declared that methods for making and screening sequence modifications and enzyme fragments were sufficiently comprehensive, routine and predictable at the time of the invention to predictably generate polymerase-encoding sequences without need of knowing which specific regions of a sequence or structure affected function or activity. Dr. Short declared that methods known at the time of the invention for modifying nucleic acid and polypeptide sequences in combination with high through-put enzyme (polymerase) screening known at the time of the invention, made methods that require previous knowledge of protein structure, including secondary or tertiary structure, active site sequences, and the like obsolete and unnecessary. Dr. Short declared that the specification sets forth an exemplary polymerase screening assay to determine if a polypeptide is within the scope of the genus used in the claimed methods (see, e.g., Example 1, of the specification). Dr. Short declared that using methods known in the art at the time of the invention it would not have been necessary to understand which specific regions of polymerase structure needed to be modified to generate a genus of nucleic acids or polypeptides for practicing the invention without undue experimentation. Dr. Short declared that the specification presented to the skilled artisan a rational and predictable scheme for making the genus of polymerases and polymerase-encoding sequences, including a rational and predictable scheme for modifying the exemplary SEQ ID

NO:1 with an expectation of obtaining a desired (e.g., new or modified or the same) function.

Dr. Short declared that the specification provided sufficient guidance to one of ordinary skill in the art to make and use the genus of polypeptides to practice the methods of the invention.

However, while not necessary, Applicants also noted that if one skilled in the art desired some structural guidance as to what amino acid substitutions could be made to make the genus of polymerase-encoding nucleic acids of the invention, such guidance could be found both in the specification and the state of the art at the time of the invention. For example, the specification in paragraph [0061], page 6, of the published specification, describes:

[0061] Additionally a “substantially identical” amino acid sequence is a sequence that differs from a reference sequence by one or more conservative or non-conservative amino acid substitutions, deletions, or insertions, particularly when such a substitution occurs at a site that is not the active site of the molecule, and provided that the polypeptide essentially retains its functional properties. A conservative amino acid substitution, for example, substitutes one amino acid for another of the same class (e.g., substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine). One or more amino acids can be deleted, for example, from a polymerase polypeptide, resulting in modification of the structure of the polypeptide, without significantly altering its biological activity. For example, amino- or carboxyl-terminal amino acids that are not required for polymerase biological activity can be removed.

Accordingly, the specification did provide guidance as to what base and residue changes could be made to make the genus of polymerase-encoding nucleic acids of the invention.

In further support of this point, i.e., that the skilled artisan using the teaching of the specification had sufficient (reasonable) guidance as to what base or amino acid substitutions could have been made to make the genus of polymerases and nucleic acids of the invention (e.g., what nucleotide substitutions could have been made to make the genus of polymerase-encoding nucleic acids of the invention), Applicants respectfully note that if the skilled artisan desired guidance as to which amino acid residues could be modified to obtain structural or functional variants of a polymerase enzyme of the invention (Applicants maintain was not necessary for one skilled in the art to be able to predict which specific regions of polymerase structure could be modified to generate a polymerase with a desired activity without undue experimentation), that information was, inter alia, readily available in the form of polymerase sequences known in the

art at the time of the invention. A routine, simple sequence alignment comparison of known polymerase sequences would have identified regions of identity and dissimilarity to provide guidance to the skilled artisan as to which sequences could be changed, or not changed, to generate structural and/or functional variations of an exemplary polymerase of the invention. As illustrated in the sequence alignment previously provided in Applicants' September 17, 2004 communication to the Office (see Appendix A of said communication) of a random selection of polymerases known in the art at the time of the invention (polymerases known prior to August 6<sup>th</sup> 1997), including the exemplary polymerase sequence of the invention (designated 1PY2\_001), regions of common structural identity between polymerases were readily identifiable. The sequence alignment highlights in colors regions of structural identity, with yellow representing regions of common structural identity between the polymerases. As defined by Wang *et al* (1989) FASEB J. 3, 14-21, there are five predicted functional domains: Region I contains two absolutely conserved aspartate residues that are in the catalytic site of all polymerases. The polymerase sequences used in the Appendix alignment belong to Type B polymerases which are replicative enzymes in Eukaryotes and most likely also Archaea. The first crystal structure of this type of polymerase came from the crystal structure of gp43 from bacteriophage RB69 (June 27<sup>th</sup> 1997, Cell 89:1087-1089). See Appendix A for detailed citations of sources of the aligned polymerases.

Furthermore, Applicants respectfully aver that if desired direction and guidance to the skilled artisan as to which base (and amino acid residues) may be modified to obtain a structural or functional polymerase variant was also readily available in the art at the time of the invention. For example, the three dimension structure of polymerases had been described, see, e.g., Wang (1997) Cell 89(7):1087-1099; Eom (1995) Acta Crystallogr. D. Biol. Crystallogr. 51(Pt 6):1086-1088, thus providing direction as to which amino acid residues can be modified and how structure correlates with function. Furthermore, at the time of the invention one of skill in the art would have been aware of the many studies of polymerase activity and active sites, see, e.g., Blasco (1993) J. Biol. Chem. 268(22):16763-16770, "Phi 29 DNA polymerase active site"; Blasco (1995) J. Biol. Chem. 270(6):2735-2740, "Primer terminus stabilization at the phi 29 DNA polymerase active site. Mutational analysis of conserved motif KXY"; de Vega (1997) J.

Mol. Biol. 270(1):65-78, "An invariant lysine residue is involved in catalysis at the 3'-5' exonuclease active site of eukaryotic-type DNA polymerases."

Accordingly, while not necessary, but if desired, one skilled in the art at the time of the invention had many sources of guidance, in addition to the specification, to determine which bases (amino acid residues) of a sequence of the invention could be modified to make, identify, screen for and use structural and/or functional variants of an exemplary polymerase of the invention without undue experimentation.

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The adequacy of a disclosure for meeting the enabling requirement of 35 USC § 112 varies with a number of factors including the predictability of the art and the breadth of the claims. *In re Wands*, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In general, the stringency of the enablement requirement increases with the unpredictability of the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ (BNA) 18, 24 (CCPA 1970). However, even in an unpredictable art, "applicants are not required to disclose every species encompassed by their claims," *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d (BNA) 1438, 1445 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ (BNA) 214, 218 (CCPA 1976)), but the disclosure must be sufficient to teach one skilled in the art "how to make and . . . use the invention as broadly as it is claimed." *Id.* And, the scope of enablement need only present a reasonable correlation to the scope of the claims. *See e.g., In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Nevertheless, not everything necessary to practice the invention need be disclosed, what is well-known may be omitted. *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation -- time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-7;

*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) (acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."). Thus, enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit.

Analogously, practitioners of the biological sciences for the instant invention also recognize the need to screen numbers of negatives to find a sample that has the desired properties, e.g., polymerase-encoding activity. Furthermore, as declared by Dr. Short, the screening procedures used to identify nucleic acids within the scope of the instant invention (e.g., identifying nucleic acids encoding polymerase active under various conditions) were all well known in the art and at the time this application was filed. These procedures comprised routine protocols for the skilled artisan. Thus, the skilled artisan using Applicants' written disclosure could practice the instant claimed invention without undue experimentation.

Accordingly, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe that the Examiner can properly withdraw the objections to the pending claims, as well as the rejection of the pending claims under 35 U.S.C. §112, first paragraph. Applicants believe that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees, outside of the three month extension of time fees, are necessitated by the present response and amendment. However, in the event any such additional fees are due, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in the connection with the filing of this document to Deposit Account No. **50-0661**, referencing docket no. **D1350-6US**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account. Please credit any overpayment to the Deposit Account.

Should any questions arise, the Examiner is invited to contact the undersigned at 858-526-5450 or [llinkowski@diversa.com](mailto:llinkowski@diversa.com).

Respectfully submitted,

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